(WO/2001/039608) ADDITION OF TETRACYCLINES TO ANIMAL FOODSTUFFS

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Abstract: A method of medicating an animal foodstuff which comprises coating particles of the foodstuff (e.g. feed pellets) with a gel containing tetracycline (e.g. chlortetracycline) and a stabilising agent. The stabilising agent is a compound containing divalent metal ions, for example a basic salt of an alkaline earth metal.

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ADDITION OF TETRACYCLINES TO ANIMAL FOODSTUFFS This invention relates to the medication of animal foodstuff materials with tetracycline antibiotics, in particular (though not exclusively) chlortetracycline.

Administration of medicaments to animals is often achieved, in cases where the medicament is to be taken orally, by integrating or mixing the medicament with the animal's foodstuff. This approach is particularly appropriate for the mass medication of a group of animals, for example a whole herd of pigs or flock of poultry, as the medicament may be incorporated in the foodstuff (feed pellets, for instance) supplied to the entire group.

One particularly useful class of drugs which are commonly administered by mass medication in this manner are the broad spectrum antibiotics of the tetracycline family, in particular chlortetracycline (CTC), which are used for the treatment and prophylaxis of a number of bacterial diseases. However, CTC is highly prone to rapid degradation when incorporated in animal foodstuff materials, and even when an excess of CTC is added to the foodstuff, there is still a substantial risk of the antibiotic potency falling below acceptable levels, particularly if the foodstuff is stored for a prolonged period and/or at an elevated temperature.

The degradation of CTC in aqueous media has been investigated and described by Katz and Fassbender (Journal of the A. O. A. C. 50 (1967) 821-827), who identified one of the principal pathways as the epimerisation to epi-CTC. This epimer is known to be toxic to many animals, a fact which makes it all the more desirable that a way be found to stabilise CTC in feed. This problem has been addressed in the past, for example in US 3, 019, 109. That patent recognises the problem of loss of CTC potency, and proposes the addition of calcium hydroxide and CTC to dried harvest mash solids, followed by a pelleting step. Thus, the active ingredient is incorporated with the food pellet ingredients at the pre-pelleting stage.

The problems associated with pre-pelleting medication are described in our earlier PCT application W096/22028. In particular, unless dedicated plant is used for specific medicated products (which is often impractical for economic reasons) batches of medicated feed tend to be manufactured using machinery normally used to produce non-medicated feed.

Scrupulous cleaning after each batch is therefore a necessity if cross-contamination is to be avoided, and the resultant extra time and effort reduces efficiency and increases operating costs.

In W096/22028 we disclosed a method for circumventing these problems by applying the medicament to feed pellets after the pelleting step, the medicament being applied in a cohesive gel carrier. We have now found that this method is particularly useful for applying CTC to animal feed pellets, as it allows the aforementioned problem of CTC instability to be largely overcome while avoiding the pre-pelleting problems which would be involved in the method of US 3, 019, 109. Initial studies focused on the use of a CTC- containing non-aqueous gel on its own, in the hope that mere exclusion of water would be sufficient to prevent epimerisation. However, although the CTC content of such a non-aqueous gel proved stable over a period of 18 months, rapid degradation occurred as soon as the gel was applied to pellets ; this was shown to be due to residual water content in the pellets. Attempts were therefore made to stabilise the CTC within the gel, and it was found that this may be achieved by the addition of divalent metal ions. Of particular utility are the salts of the Group II elements such as calcium and magnesium, and especially basic salts such as hydroxides, oxides and carbonates. By using a cohesive non-aqueous gel containing both CTC and divalent metal ions it was found that coated feed pellets could be produced in which the CTC is distributed uniformly throughout the feed pellet batch and the rate of epimerisation is significantly retarded.

Thus, in one aspect the invention provides a method of medicating an animal foodstuff material comprising the step of coating particles of said foodstuff material with a gel containing a tetracycline (or a pharmaceutically acceptable salt or derivative thereof) and a compound containing divalent metal ions. Preferably, the gel is non-aqueous and the tetracycline is chlortetracycline.

The divalent ions of the alkaline earth (Group II) metals have been shown to be effective in the method of the invention, especially calcium and magnesium. The source of the ions appears to be unimportant, and while it will doubtless normally be convenient to supply the ions in the form of ionic salts, complexes may also be of use. The use of the term"compound"herein is therefore to be understood as including complexes.

The invention additionally extends to the finished feed pellets coated by the method described above. After the gel coating has been applied, the suspension medium may be absorbed into the pellets to a greater or lesser extent, with the beneficial effect that the pellets dry and harden somewhat. Depending upon the precise transport properties of the pellet ingredients, the residual components of the gel (i. e. the CTC, divalent metal ions and gelling agent) tend to be retained at or towards the surface of the pellets. Accordingly, the finished pellets are physically distinguishable from those in which CTC has been added at the pre-pelleting stage (for example as in US 3, 019, 109) and the invention therefore provides, in alternative aspect, a particulate animal foodstuff material, the individual particles of said foodstuff material having a surface layer containing a tetracycline (or a pharmaceutically acceptable salt or derivative thereof), a compound containing divalent metal ions and a gelling agent.

In a further aspect, the invention provides a composition for coating particulate animal foodstuffs, the composition comprising a suspension medium, a gelling agent, a tetracycline (or a pharmaceutically acceptable salt or derivative thereof) and a compound containing divalent metal ions.

By utilising the gel coating technology of our earlier application W096/22028, all of the advantages described therein are attained. Most importantly the technique provides a reliable method for accurately and homogeneously incorporating a defined dosage of CTC with a known quantity of feed pellets. Furthermore, because of the nature of the gel, the mixing vessel tends to be left substantially free of CTC contamination after use.

In this specification, the term"gel"is to be understood as referring to any viscous cohesive suspension, and the term"gelling agent"to any thickening agent capable of producing such a suspension. The gel is preferably a highly viscous solution or suspension having low flow and good adhesive properties. Thixotropic gels are particularly preferred. Examples of suitable gelling agents which may be used are modified cellulose polymers, synthetic polymers, natural polysaccharides, clays, proteins and colloidal silica, but other gelling agents may also be used.

The suspension medium may be provided by any suitable non- aqueous liquid ; natural vegetable oils such as soya oil are preferred.

In accordance with expectations, the stabilisation effect appears to increase with increased concentration of divalent ions. However, in tests using calcium hydroxide we encountered problems in controlling the viscosity of the gel when concentrations greater than 15% w/w were employed, with the effect that handling and pumping of the gel became difficult. The most effective range of concentrations for calcium hydroxide appears to be 1 to 15% w/w, with the range 5 to 10% w/w being preferred.

From our tests using calcium hydroxide it appears that the particle size may have a significant effect on the degree of CTC stabilisation, with more finely divided particles being distinctly to be preferred.

We have also found that stabilisation of CTC in the gel may be enhanced by the addition of a small amount of an antioxidant. Tests were carried out using butylated hydroxytoluene (BHT). A significant retardation in epi-CTC formation was noted at concentrations up to 0. 02%, with a rather less marked increase in stability at higher concentrations. As 0. 02% BHT is the normally recommended maximum concentration of BHT, this is taken to be the optimum amount. Other oil-soluble antioxidants (such as ascorbyl palmitate) may also be used, preferably at their maximum recommended concentrations.

Although we refer throughout this specification to chlortetracycline, the similarities in structure and chemistry between the various tetracyclines means that the method of the invention will be of benefit across the whole class of such compounds. Thus, the references to CTC should not be seen as limiting the scope of the invention to that particular compound.

The invention will hereinafter be described in more detail by way of example only, with reference to the various experimental trials described below.

As a preliminary step, we sought to establish the stability of CTC in a non-aqueous gel, both in bulk gel itself and in gel applied to animal feed pellets. We therefore formulated a gel containing 10% CTC, 5% silica, 0. 01% BHT and soya oil (to 100%). The CTC content of the gel was tested using a standard reverse phase hplc procedure over a period of 18 months, and found not to decline appreciably. However, when the same gel was applied to animal feed pellets, rapid epimerisation occurred. A trial was carried out at ambient temperature (approximately 20°C) using pellets from BOCM Pauls, figures for epimer formation over a period of one month being set out in Table 1 below : Table 1 Epimer formation in non-stabilised gel-coated pellets No. of days after Percentage trial commencement epi-CTC 1 4. 9 12 31. 4 17 33. 2 31 43. 3 By the end of the trial, the amount of epi-CTC was approaching equilibrium concentration.

The speed of degradation was found to be heavily dependent upon the degree of moisture content in the pellets. This

was established by conducting parallel tests using two different types of feed pellets having widely different water contents : Rowetts pellets having a water content of 8. 03% and BOCM pellets having a water content of 13. 63%. The gel contained 10% CTC, 4t silica, 0. 01% BHT and soya oil (to 100W), and the trial was conducted at ambient temperature (approximately 20°C). The results are shown in Table 2 below : Table 2 Moisture dependency of epi-CTC formation No. of days after Percentage % water trial commencement epi-CTC content Rowetts : 1 3. 6 8. 03 9 5. 3 T 13 5. 0 BOCM : 3 2. 9 13. 63 9 15. 3 12 17. 4 The rate of epi-CTC formation was also found to be temperature dependent, as will be seen from the results in Table 3 below, which were obtained using a gel containing 10% CTC, 5% silica and 0. 010-. BHT in soya oil and pellets from BOCM Pauls : Table 3 Temperature dependence of epi-CTC formation Temp. Initial conc. Conc. CTC after Initial % epi-CTC (°C) CTC (ppm w/w) 24hrs (ppm w/w) epi-CTC after 24h 5 354. 98 328. 60 1. 47 3. 4 25 354. 98 265. 48 1. 47 19. 3 40 354. 98 194. 09 1. 47 40. 0 The stabilising effect of calcium hydroxide was tested at various different concentrations. Three gels containing 10% CTC and 6% silica in soya oil were produced, being identical except for their differing Ca (OH) 2 concentrations (1, 2 and 3% w/w respectively), the Ca (OH) 2 being supplied by BDH. Additionally, a fourth gel was produced containing 10W CTC, 5% silica and 0. 010-. BHT in soya oil. Each of the gels was coated onto pellets obtained from BOCM Pauls, which were then stored for 8 days at 25°C. The amounts of epimer present in the samples at the end test were as shown below in Table 4 : Table 4 Effect of Ca (OH) 2 concentration on epi-CTC formation

 Calcium hydroxide Amount of

 content (s w/w) epi-CTC (% w/w) 0 28. 6 1 16. 9 2 11. 8 5 8. 6 A further comparative test was carried out using a gel containing 10% w/w calcium hydroxide from BDH. In this trial the concentration of epimer was found to be 10. 7% after 5 days and 19. 5% after 11 days.

Tests with calcium hydroxide were carried out using samples obtained from different suppliers and having significantly different particle sizes. The average particle diameter in the Ellis & Everard product was substantially larger than that of the BDH product. Two identical gels containing 10% CTC, 5% silica and 0. 01% BHT in soya oil were produced, differing only in that 5% w/w Ca (OH) 2 from Ellis & Everard was incorporated in one and 5% w/w Ca (OH), from BDH in the other. The gels were then applied to pellets from BOCM Pauls and the rate of epimerisation measured in terms of the percentage of epimer present after 3 days and 7 days. The results appear in Table 5 below : Table 5 Effect of Ca (OH) 2 particle size on CTC stabilisation Source of W epi-CTC W epi-CTC Ca OH 2 after 3 days after 7 days Ellis & Everard 5. 0 17. 9 BDH 4. 9 11. 4 The additional stabilising effect of added antioxidant was investigated using four identical gels containing 10% w/w calcium hydroxide supplied by Croxton & Garry, 10 CTC and 6% silica in soya oil, the gels differing only in their antioxidant content (0, 0. 02%, 0. 04% and 0. 06% BHT respectively). The gels were coated onto pellets supplied by BOCM Pauls, and the test conducted at ambient temperature (approximately 20°C). The rate of epimerisation was measured in terms of the amount of epi-CTC present in the samples after 6 days and after 15 days. The results are given in Table 6 below : Table 6 Additional stabilisation effect of antioxidant Antioxident % epi-CTC % epi-CTC (BHT-% w/w) after 6 days after 15 days 0 19. 3 31. 4 0. 02 8. 7 20. 4 0. 04 8. 2 21. 9 0. 06 8. 1 14. 2 The following is an example of a gel manufactured in accordance with the invention, which was coated onto feed pellets (BOCM Pauls) and tested for epi-CTC formation at ambient temperature (around 20°C) over a prolonged period : Example 1 Calcium hydroxide The gel was made up as follows : wt % Chlortetracycline 10% Calcium hydroxide 10t Silica (Aerosil 200) 5. 0t BHT 0. 010-.

Soya oil to 100% The amounts of epi-CTC found over the course of the test are shown in Table 7 below : Table 7 Results of test on Example 1 No of days after commencement of trial % epi-CTC present 14 2. 8 22 11. 00 30 17. 08 78 22. 29 Example 2 Magnesium hydroxide Parallel trials were carried out at two different storage temperatures (25°C and 40°C), using a gel containing 5% w/w Mg (OH) 2 coated onto pellets supplied by BOCM Pauls, with CTC content being measured at the start of the trial and at days 4 and 5. The results are shown in Table 8 below : Table 8 Results of tests on Example 2 Days after CTC content Percentage commencement (g g-1) epi-CTC Initial 545. 199 3. 6 Storage at 25°C 4 498. 628 8. 8 5 481. 890 16. 9 Storage at 40°C 4 259. 691 30. 7 5 208. 345 29. 8

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Claims 1. A method of medicating an animal foodstuff material comprising coating particles of said foodstuff material with a gel containing a tetracycline (or a pharmaceutically acceptable salt or derivative thereof) and a compound containing divalent metal ions.

2. A method according to Claim 1, wherein the gel is non- aqueous.

3. A method according to Claim 1 or Claim 2, wherein said tetracycline is chlortetracycline.

4. A method according to any of Claims 1 to 3, wherein said compound containing divalent metal ions is selected from the compound of alkaline earth metals.

5. A method according to Claim 4, wherein said alkaline earth metal is magnesium or calcium.

6. A method according to Claim 4 or Claim 5, wherein the compound is a hydroxide, oxide, carbonate or other basic salt.

7. A method according to Claim 6, wherein said compound is calcium hydrcxide (Ca (OH)).

8. A method according to Claim 7, wherein the calcium hydroxide is present at a concentration in the range 1 to 15% (w/w). 9. A method according to Claim 7, wherein the calcium hydroxide is present at a concentration in the range 5 to 10% (w/w).

10. A method according to any preceding claim, wherein the gel further contains an antioxidant.

11. A method according to Claim 10, wherein the antioxidant is butylated hydroxytoluene (BHT).

12. A method according to Claim 11, wherein BHT is present in a concentration of up to O. 02% (w/w).

13. A particulate animal foodstuff material, the individual particles of which have a surface layer containing a tetracycline (or a pharmaceutically acceptable salt or derivate thereof), a compound containing divalent metal ions and a gelling agent.

14. A composition for coating particulate animal foodstuffs, the composition comprising a suspension medium, a gelling agent, a tetracycline antibiotic and a compound containing divalent metal ions.

15. A method substantially as hereinbefore described, with a reference to any of the examples.

16. A particulate animal foodstuff material substantially as hereinbefore described, with reference to any of the examples.

17. A composition for coating particulate animal foodstuffs, substantially as hereinbefore described, with reference to any of the examples.